REMARKS

Claims 2-7 and 9 are pending in the instant application. Claims 2-5, 7 and 9 have been amended to indicate that EPO can be used to enhance the function of "injured" tissue. Support for the amendment is found at page 20, lines 15-26 and page 4, lines 14-18. No new matter has been added by these amendments which capture subject matter the Examiner has indicated is enabled[2].

Claims 2-5, 7, and 9 have also been amended to clarify the claim language by deleting redundant language in the claims. No new matter is added by the foregoing amendments.

Entry of the amendments and the remarks made herein into the record of the above-identified application is respectfully requested. Applicants believe that the amendments and remarks made herein place all pending claims in condition for allowance.

THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT SHOULD BE WITHDRAWN

Claims 1-7, and 9 are rejected under 35 U.S.C. § 112, first paragraph, because the Examiner contends that while enabled for normal and injured tissue, the claimed methods are not enabled for the full scope of enhancing the function of *damaged* excitable tissue, because damaged excitable tissue is allegedly the end result of many diseases. During the in person interview of November 22, 2004, Examiner DeBerry and Examiner Kemmerer indicated that the amended claims would be favorably considered in light of the submission of references showing the successful use of EPO to enhance function of damaged tissue.

With respect to enhancing the function of damaged excitable tissue, Applicants invite the Examiner's attention to the following studies published subsequent to the filing date of the present application which demonstrate that the claimed methods are enabled:

[2] The Examiner has already indicated that the claimed methods are enabled for enhancing the function of normal or injured excitable tissue (see page 3, lines 3-5, of the Office Action dated July 15, 2003 and page 3, lines 1-5 of the Office Action dated October 26, 2004). Therefore, Claims 1-5, 7 and 9 have been amended to recite injured tissue.

Ehrenreich *et al.,* 2002, Molec. Med. 8:495-505 ("Ehrenreich");

Bianchi *et al.*, 2004, Proc. Natl. Acad. Sci. USA. 101:823-282 ("Bianchi"); and

Agnello *et al.*, 2002, Brain Res. 952:128-134 ("Agnello").

Ehrenreich, a reference co-authored by the inventors, peripherally administered high doses of EPO within 5 hours of onset of symptoms in human stroke patients and showed an association between EPO administration an improved outcome. Fifty-three patients with ischemic stroke were examined for neurological deficits using stroke scales (NIH and Scandinavian Stroke Scale) for neurologic scoring (see page 496, column 2, final paragraph). Neurologic scoring was performed to assess neurological damage before treatment with EPO, and at 3, 7, 18 and 30 days following EPO administration (see page 498, column 1, center paragraph). The recovery of EPO treated patients based on neurologic scoring shown in Fig. 2A and 2B, at page 500, demonstrates that EPO administration effectively enhanced the function of damaged human neural tissue in comparison to stroke patients administered a placebo or low dose of EPO. The stroke scales used in the measurement of recovery are based on levels of consciousness and various motor skills which are indicative of functional outcome. Thus, the results demonstrate that the peripheral administration of effective doses of EPO effectively enhanced the function of damaged excitable central nervous system tissue, thereby enhancing neurological function, including brain function, in patients with damaged excitable tissue.

Bianchi, a reference co-authored by the inventors, shows that peripherally administered EPO prevented and reversed nerve, *i.e.,* excitable tissue, dysfunction caused by streptozotocin (STZ)-induced diabetes in rats. In the STZ diabetes model, rats developed mechanical dysfunction and thermal sensation (nociception) dysfunction. The thresholds of dysfunction were measured by antidromic tail-nerve conduction and by exposing a hind paw

to a heated surface and recording time for withdrawal (see page 824, 2nd half of column 1 and paragraph abridging cloumns 1 and 2). In Bianchi, EPO was peripherally administered after a five week delay after STZ-induction of diabetes. This allowed for the onset of neurological damage associated with diabetes prior to treatment with peripherally applied EPO. Such treatment was continued for five weeks (therapeutic schedule) (see page 824, top of column 1).

The results of the therapeutic schedule of EPO administration demonstrate that by 9 weeks after STZ administration to induce diabetes, EPO treated rats exhibit significant restoration of the dysfunction of mechanical and thermal mociception cause by diabetes in comparison to diabetic rats that were not treated with EPO (see page 824, column 2 through page 825, column 1 and Fig. 2B). Bianchi also examined the density of intraepidermal nerve fibers and found a significant decrease in density by five weeks after induction of diabetes in rats not treated with EPO. In contrast, diabetic rats administered the therapeutic schedule of EPO exhibited a complete reversal of loss of nerve density (see page 825, top of column and page 826, Fig. 5A-5D 2). These results clearly demonstrate that peripheral administration of effective doses of EPO can be used to enhance the function of damaged excitable tissue in a mammal, where the damage results from disease.

Agnello, a reference co-authored by the inventors, used a rat model to induce experimental autoimmune encephalomyelitis (EAE) by administering myelin basic protein (MBP). High doses of EPO were then administered beginning at three days after MBP administration. The rats were scored for symptoms of EAE including neurological factors such as flaccid tail and hind limb paralysis, where higher scores are indicative of increasing amounts of damage to factors (see page 129, column 1 and top of column 2). The results shown in Fig. 1 at page 130 demonstrate that in an animal model for autoimmune disease EPO repairs the function of damaged tissue in comparison to the control rats which exhibited

higher EAE scores. Thus, Agnello demonstrates that one skilled in the art can peripherally administer an effective dose of EPO and successfully enhance the function of damaged excitable peripheral nervous system tissue, caused by disease.

The experimental results described above demonstrate the efficacy of the claimed methods in animal models, and in human subjects, for a number of different conditions involving tissue damaged as a result of various diseases. Thus, the claims are enabled and the rejection under 35 U.S.C. § 112 should be withdrawn.

CONCLUSION

Entry of the foregoing amendments and remarks into the record of the above-identified application is respectfully requested. Applicants estimate that the remarks made herein place the pending claims in condition for allowance. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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